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August 30, 1994

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Docket No. 78N-036L; 58 Fed. Reg. 46589 (Sept. 2, 1993), Laxative Drug Products for Over-the-Counter Human Use; Proposed Amendment to the Tentative Final Monograph

Ladies and Gentlemen:

Submitted herewith in triplicate are new data in response to the notice of proposed rulemaking published in the Federal Register (58:46589-96) on September 2, 1993, pertaining to the classification of docusate sodium, calcium and potassium as Category I stool softener laxative ingredients. The undersigned requests that the monograph be amended to include the combination of the stimulant laxative, bisacodyl, with docusate sodium. Portions of this document are proprietary to CIBA Consumer Pharmaceuticals and Ciba-Geigy Corporation and are clearly marked "CONFIDENTIAL". We respectfully request these documents NOT be made available for public access.

ACTION REQUESTED

CIBA Consumer Pharmaceuticals requests that the Commissioner issue an amendment to the monograph's section detailing the permitted combinations of stimulant and stool softener laxative active ingredients, 21 CFR Part 334.30 (i) to include the stimulant laxative, bisacodyl. The amendment would change the monograph wording as follows:

"Part 334- LAXATIVE DRUG PRODUCTS FOR THE OVER-THE-COUNTER HUMAN USE"

"Section 334.30 Permitted combination of active laxative ingredients.

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"Subsection 334.30 (i) The following stool softener laxative ingredient may be combined with the following stimulant laxative ingredients provided the combination is labeled according to §§ 334.60 and 334.62:

(4) Docusate sodium identified in § 334.20(c) and bisacodyl identified in § 334.18(b)."

In support for the combination of docusate sodium and bisacodyl, we include in this submission data that were originally filed to FDA in 1969 as part of an IND for the combination. As you will find, animal toxicology studies and human clinical trials have been performed on this combination to adequately document its safety and effectiveness. Moreover, each of the two component active ingredients (docusate sodium and bisacodyl) are already generally recognized as being safe and effective for OTC use in the OTC laxative tentative final monograph.

Introduction

On September 2, 1993 the FDA published a notice of proposed rulemaking to amend the Tentative Final Monograph (TFM) for over-the-counter (OTC) laxative drug products. This proposed amendment includes conditions under which docusate salts are generally recognized as safe and effective and are not misbranded (Category I) as stool softeners. The FDA is allowing docusate salts to be formulated alone or in combination with certain stimulant, bulk forming and hyperosmotic laxatives in oral dosage forms. The ingredient bisacodyl was not included in the list of allowable stimulant laxative combinations (listed were casanthranol, phenolphthalein and sennosides A and B).

CIBA Consumer Phamaceuticals is proposing that the combination of docusate sodium and bisacodyl be permitted for three reasons. First, each ingredient is Category I (safe and effective) in the Tentative Final Monograph. Second, the proposed bisacodyl and docusate sodium combination meets the criteria for Category I combinations as set forth in the 1975 Proposal to Establish Monographs for OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Products (40 FR:No. 56, March 21, 1975, 12921). Third, the additional attached data support the combination.

This combination will be labeled in accordance with 21 CFR § 334.50, 334.60 and 334.62.

Basis for Combination Therapy

The primary diphenylmethane cathartics are phenolphthalein and bisacodyl. These agents have similar pharmacological characteristics and clinical uses[1]. Phenolphthalein's chemical structure is also similar to that of bisacodyl[2]. Therefore, one would not expect a difference in the pharmacology, toxicology, stability or compatibility of the combination of bisacodyl and docusate sodium from the already-allowable combination of phenolphthalein and docusate.

The fact that there are already a number of products on the market that contain the combination of phenolphthalein and docusate sodium also provides evidence that the proposed combination is safe and effective, and provides a benefit to consumers. Among these products are Correctol®, Extra Gentle Ex-Lax ® and Feen-A-Mint®.

It is noteworthy that Boehringer Ingelheim, the previous owner/manufacturer of Dulcolax®, manufactured and marketed a combination product that contained docusate sodium and bisacodyl in Canada. This product was marketed from 1985-1986 but was discontinued due to poor sales performance.

Preclinical toxicology and clinical data are available for the proposed combination and were previously submitted to FDA via an IND for this combination. Attached are summaries as well as full reports for these studies found in Sections III and IV. Please note that the term "DOSS" appears in several of the documents. This term is an abbreviation used for the docusate sodium portion of the combination product. Overall, the data demonstrate that the combination provides a safe added benefit over administration of bisacodyl alone. Moreover, this combination of ingredients provides a rational therapeutic benefit for people suffering from hard stools, a frequent condition associated with constipation.

Limited stability data are also available for the combination of bisacodyl and docusate sodium which demonstrate the compatibility of the two active ingredient components. A tablet dosage form of product was packaged in amber glass bottles with screw caps for 12 months at 6°, 25° and 40° Celsius. Data show that after 12 months storage at 6° and 25° Celsius, the tablets met all specifications. Tablets held at 40° Celsius at 3 months were found to be within specification. The tablets did appear to slightly change color. After 3 months, the tablets held at 40° Celsius did tend to harden or "set-up" resulting in tablets which did not pass the disintegration test. These data are included herein as Section V.

In addition, an extensive literature database search was performed to obtain any available information pertaining to the safety and effectiveness of the bisacodyl and docusate sodium combination. The following sources were queried: Medline, Embase and Biosis from 1966 to present. No literature citations were found.

Conclusion

Since the combination of bisacodyl and docusate salts meet the three criteria outlined in the second paragraph of the INTRODUCTION section, Category I status in the OTC laxative monograph should be granted.

If there are any questions pertaining to this submission, please contact the undersigned at (908) 602-6706 or via facsimile at (908) 602-6612.

Sincerely,

CIBA Consumer Pharmaceuticals
Division of Ciba-Geigy Corporation

Vincent De Stefano
Manager, Regulatory Affairs

Bibliography

1) Goodman and Gilman; The Pharmacological Basis of Therapeutics, 6th Edition:1006, 1980.

2) Goodman and Gilman; The Pharmacological Basis of Therapeutics, 6th Edition:1007, 1980.

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EXECUTIVE SUMMARY

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